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## SEARCH REQUEST FORM

OCT 23 1992

Scientific and Technical Information Center

Requester's Full Name: Kathleen Kerr Examiner #: 77468 Date: 10/22/02  
Art Unit: 1652 Phone Number 305-1229-7 Serial Number: 697768479  
Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. *mes*

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): *all attached* \_\_\_\_\_

Earliest Priority Filing Date: \_\_\_\_\_

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please do a structure search of the compound  
of claim 107.

If no art before 1/24/00, please search for generic  
methotrexate — dexamethasone compounds  
Dex-Y-Mtx (where Y is  $\phi$   
or anything)

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## STAFF USE ONLY

## Type of Search

## Vendors and cost where applicable

Searcher: <u>Sheppard</u>	NA Sequence (#) _____	STN _____
Searcher Phone #: <u>808-4499</u>	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: <u>10/24/02</u>	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: _____	Other _____	Other (specify) _____

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FILE 'HCAPLUS' ENTERED AT 15:51:50 ON 26 OCT 2002

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FILE COVERS 1907 - 26 Oct 2002 VOL 137 ISS 18  
FILE LAST UPDATED: 25 Oct 2002 (20021025/ED)

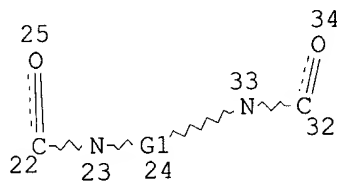
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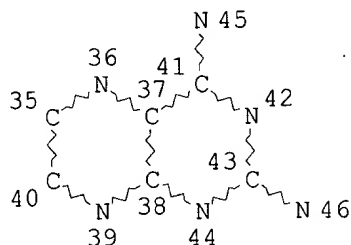
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L13 STR



= Y



= MTX

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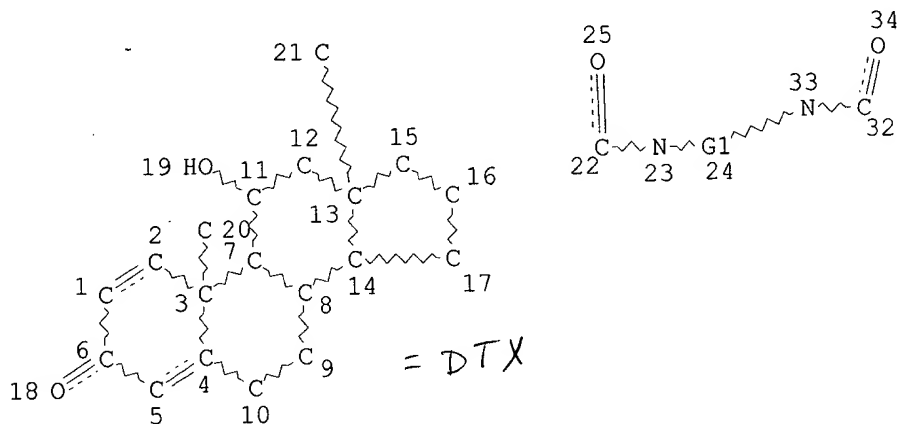
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

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NUMBER OF NODES IS 19

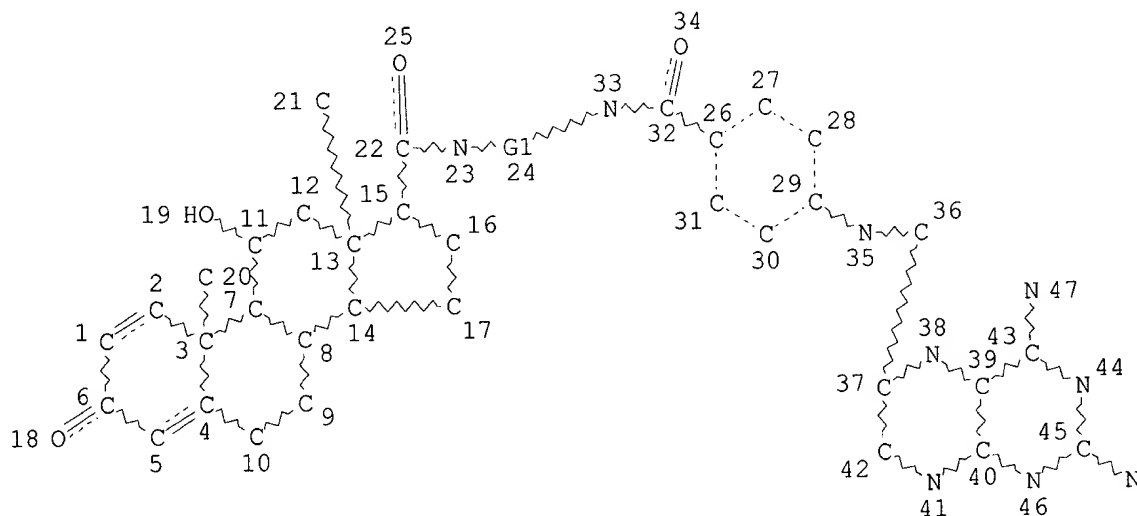
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L15 STR



REP G1=(0-10) C  
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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE  
L18 172 SEA FILE=REGISTRY SSS FUL L13 OR L15  
L19 STR



Page 1-A

48

Page 1-B  
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
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NUMBER OF NODES IS 48

STEREO ATTRIBUTES: NONE  
L20 2 SEA FILE=REGISTRY SUB=L18 SSS FUL L19  
L21 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L20

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L21 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:31914 HCAPLUS  
DOCUMENT NUMBER: 136:98820  
TITLE: Yeast three-hybrid system for in vivo drug screening  
and enzyme evolution using chemical inducers of  
dimerization  
INVENTOR(S): Cornish, Virginia W.  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 48 pp., Cont.-in-part of U.S.  
Ser. No. 490,320.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002004202	A1	20020110	US 2001-768479	20010124
PRIORITY APPLN. INFO.:			US 2000-490320	A2 20000124

AB The disclosed invention relates to the evolution of enzymes in vivo, and drug screening in vivo through the use of chem. inducers of protein dimerization. The subject invention provides a compd. having the formula: H1--X--B--Y--H2 wherein each of H1 and H2 may be the same or different and capable of binding to a receptor which is the same or different; wherein each of X and Y may be present or absent and if present, each may be the same or different spacer moiety; and wherein B is an enzyme cleavable moiety. This invention also provides a method of screening proteins for the ability to catalyze bond cleavage or bond formation, comprising the steps of: (a) providing a cell that expresses a pair of fusion proteins which upon dimerization change a cellular readout; (b) providing the compd. of the invention which dimerizes the pair of fusion proteins, said compd. comprising two portions coupled by a bond that is cleavable or formed by the protein to be screened; and (c) screening for the cellular readout, wherein a change the cellular readout indicates catalysis of bond cleavage or bond formation by the protein to be screened. However, it has not heretofore been suggested to use small mol. induced protein dimerization to screen for catalysis in vivo., and specifically, it has not been suggested to use an enzyme cleavable moiety to link two mols. to dimerize proteins. This invention provides proteins de novo with prescribed binding and catalytic properties and permits screening cDNA libraries based on biochem. function. Practically, we believe that powerful screens in combination with existing randomization techniques will make it possible to take an existing protein fold and evolve it into an enzyme with a new function generating useful catalysts for the pharmaceutical and chem. industries. Since the screen is done in vivo and in both prokaryotes and eukaryotes, the methodol. can be applied to functional genomics and drug discovery. A new chem. inducer of

dimerization (CID) was recently developed in Professor Cornish's lab, which uses a heterodimer of methotrexate (MTX) and dexamethasone (DEX) which, when placed in the yeast three-hybrid system, reconstitutes transcription of the lacZ gene. The effects of altering the structure of the DEX-MTX CID and the protein chimeras in the three-hybrid assay were investigated. It was obsd. that all DEX-MTX CIDs, except the DEX-MTX CID with the shortest chem. linker, showed the ability to induce .beta.-galactosidase levels at levels 400% above strains possessing no CID. The DEX-MTX CIDs showed little or no increase in .beta.-galactosidase levels above background levels in strains where dihydrofolate reductase (DHFR) from E. coli was replaced by DHFR from murine. The three-hybrid system did show some directional preference to the way in which the receptors were fused to the DNA binding domain and the activation domain. These studies have led to a better understanding of the factors that are important in activating transcription in the DEX-MTX yeast three-hybrid system.

IT 389085-38-5

RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(yeast three-hybrid system for in vivo drug screening and enzyme evolution using chem. inducers of dimerization)

L21 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:545747 HCAPLUS

DOCUMENT NUMBER: 135:133932

TITLE: An in vivo screen using chemical inducers of dimerization

INVENTOR(S): Cornish, Virginia W.

PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA

SOURCE: PCT Int. Appl., 123 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053355	A1	20010726	WO 2001-US2285	20010124
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2000-490320 A 20000124

AB The subject of the invention provides a compd. having the formula: H1-X-B-Y-H2, wherein each of H1 and H2 may be the same or different and capable of binding to a receptor which is the same or different; wherein each of X and Y may be present or absent and if present, each may be the same or different spacer moiety; and wherein B is an enzyme cleavable moiety. Said compds. can be called chem. inducers of dimerization. This invention also provides a method of screening proteins for the ability to catalyze bond cleavage.

IT 351419-40-4

RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(comps. comprising receptor-binding moiety, spacer and enzyme  
cleavable moiety for screening drugs and proteins capable of catalyze  
bond cleavage)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS  
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=> fil caold  
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FILE COVERS 1907-1966  
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate  
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assignees, and patent information, e.g., patent numbers, are  
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Property values tagged with IC are from the ZIC/VINITI data file  
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STRUCTURE FILE UPDATES: 25 OCT 2002 HIGHEST RN 466118-13-8  
DICTIONARY FILE UPDATES: 25 OCT 2002 HIGHEST RN 466118-13-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when  
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

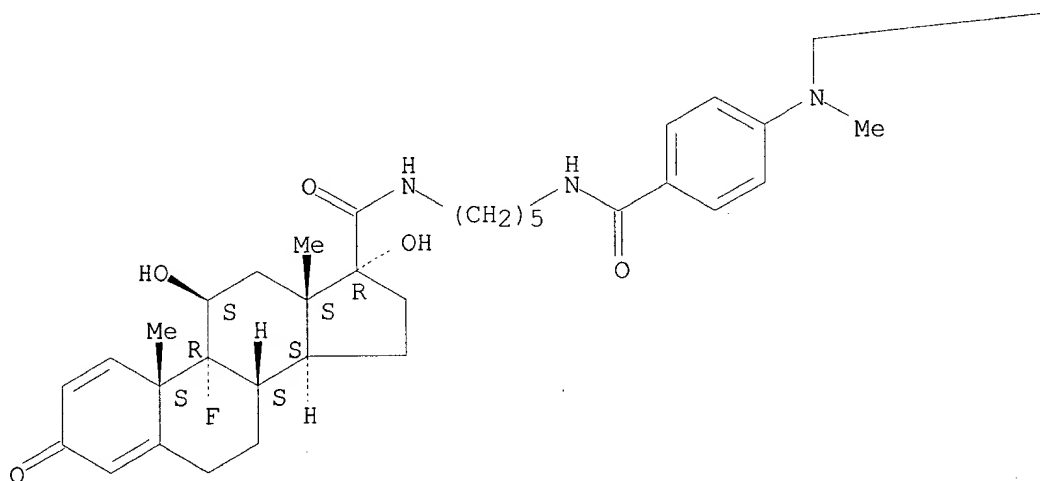
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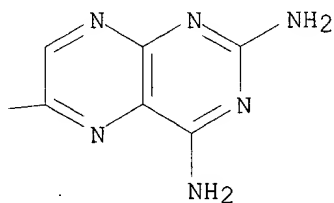
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 RN 389085-38-5 REGISTRY  
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 FS STEREOSEARCH  
 MF C40 H50 F N9 O5  
 SR CA  
 LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

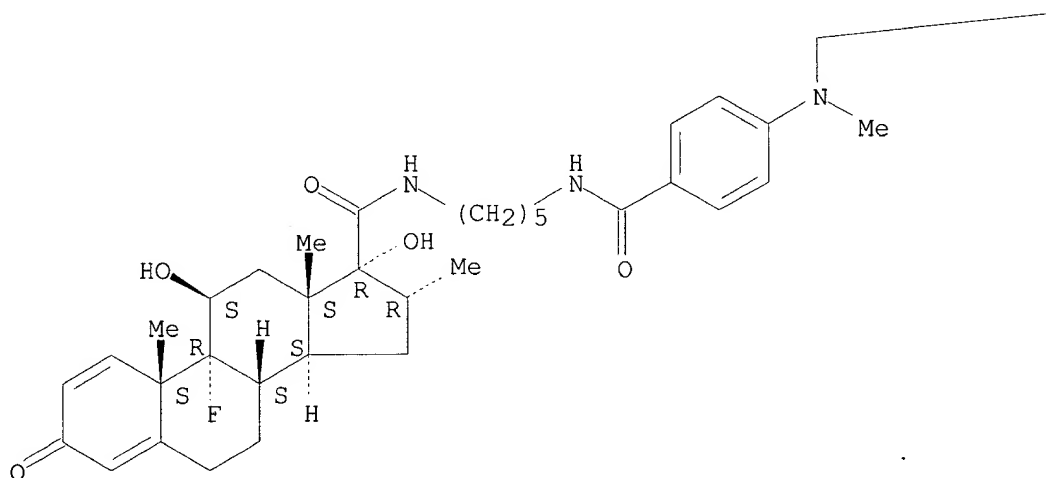
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REFERENCE 1: 136:98820

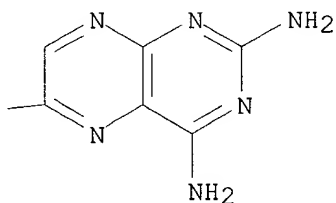
L20 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS  
 RN 351419-40-4 REGISTRY  
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 LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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